Molecular Mechanisms of Stem Cells Pluripotency and Cell Fate Specification

Findlay, Greg M.; David, Laurent; Beyer, Tobias A.

Published in:
Journal of Molecular Biology

DOI:
10.1016/j.jmb.2017.03.011

Publication date:
2017

DOi: 10.1016/j.jmb.2017.03.011

Molecular Mechanisms of Stem Cells Pluripotency and Cell Fate Specification

Greg M. Findlay[1], Laurent David[2,3] and Tobias A. Beyer[4]

[1] The MRC Protein Phosphorylation and Ubiquitylation Unit, School of Life Sciences, The University, of Dundee, Dundee, DD1 5EH, UK, g.m.findlay@dundee.ac.uk
[2] INSERM UMS 016, SFR Francois Bonamy, iPSC core facility, Nantes, F-44000 France; CNRS UMS 3556, Nantes, F-44000 France; Université de Nantes, Nantes, F-44000 France; CHU de Nantes, Nantes, F-44000 France;
[3] INSERM, Center for Research in Transplantation and Immunology (CRTI) U1064, Nantes, F-44000 France; Université de Nantes, UMR 1064, Nantes, F-44000 France; laurent.david@univ-nantes.fr
[4] Institute for Molecular Health Sciences, Department of Biology, ETH Zurich, Switzerland, tobias.beyer@biol.ethz.ch

Over the past three decades, scientists have realized that stem cells will play a central role in future therapies. These cells have key functions in tissue homeostasis and upon injury can replenish injured tissue. Aberrant activation of stem cells leads to disease such as cancer and degenerative diseases. However, in order to bring stem cells to the clinic, a profound understanding of the molecular regulation of these cells is a prerequisite. Here, in this special issue, we present a series of reviews summarizing recent advances in molecular mechanisms of stem cell pluripotency and cell fate specification.

Pluripotency is a transient feature of cells residing in the inner cell mass of a developing blastocyst and is defined as the ability of a cell to contribute to all germ layers of the embryo. This plastic state can be captured *in vitro* and conserved as Embryonic Stem Cells (ESCs) under suitable culture conditions. These cells remain pluripotent and are able to self-renew indefinitely *in vitro* [1]. Mouse ESCs were first derived from blastocysts in the early 1980s [2, 3], whilst in 1998 the Thomson laboratory derived human ESCs for the first time [4]. More recently, Yamanaka and colleagues achieved **THE** breakthrough in pluripotency research when they reported reprogramming of somatic mouse [5] and human [6] cells to an ESC-like state. And so the term induced pluripotent stem cells (iPSC) was coined.

Capturing pluripotent stem cells in the laboratory has allowed researchers to delineate signaling cues and molecular mechanisms responsible for stem cell maintenance and cell fate specification. In parallel, a major research effort was initiated to unveil the enormous potential of pluripotent cells for regenerative/personalized medicine. In recent years, seminal studies defined and refined conditions for deriving clinically relevant cell populations from pluripotent cells, including cardiomyocytes, cells of the

peripheral and central nervous system, hepatocytes and pancreatic □-cells (for a review see: [7]). The advent of human ESCs and iPSCs thereby opened unprecedented opportunities for future therapeutics, regenerative medicine, drug screening and modeling of human diseases.

In this special issue of the Journal of Molecular Biology, we focus on research which elucidates fundamental biological mechanisms using stem cells and their derivatives as model systems. So far, pluripotent stem cells provide us with a model to fill the void in our knowledge of early human development. Furthermore, stem cells give us the great opportunity to study basic molecular mechanisms such as cell signaling, epigenetics, RNA interference and transcriptional regulation in an undisturbed genome, in contrast to cancer cell lines.

In the first review of this special issue, Jörg Betschinger [8] gives an overview on an emerging question in stem cell biology: How is pluripotency network dissolution controlled to enable cells to differentiate efficiently towards the three embryonic germ layers. This has implications far beyond simple development, as correct resolution of the pluripotent state towards differentiation is crucial for cells to be safely applied in therapeutics. Linking the molecular framework described over recent years to cell fate specification in the early murine embryo, he raises important questions to be addressed in future studies.

Reviews by the Navarro, Baubec and Wutz laboratories shift the focus towards epigenetic regulation of gene expression using pluripotent stem cells as a model system [9, 10] Wutz: not yet available). The Navarro lab proposes a novel concept that ESCs present an “epigenetic paradox”: They are stably captured in a self-renewing state which maintains their identity. However, this state is not entirely dependent on classical epigenetic mechanisms but rather is stabilized by transcription factors and a particular chromatin state dependent on extrinsic signalling [10]. In a similar vein, reviews by the Baubec and Wutz laboratories provide insights into the mechanisms and dynamics of DNA methylation and facultative heterochromatin formation using mESCs as model system. These processes are essential for correct cell fate specification and mis-regulation has been implicated in cancer.

The last set of reviews discusses recent insights into emerging molecular mechanisms of post-transcriptional/translational regulation of pluripotency. The Findlay laboratory provides an overview of kinase signaling networks, many of which have been studied in disease systems rather than in pluripotency (Ref not on Pubmed yet). Interestingly, they focus on novel kinase cascades and those implicated in the cell cycle, DNA damage response, nutrition sensing, metabolism and cell stresses and thereby provide a new perspective on these core cellular processes in the context of pluripotency. RNA interference (RNAi) is another crucial post-transcriptional mechanism to fine-tune gene expression programs. small RNAs together with their effector proteins have been shown to play essential roles in pluripotency and cell fate specification. The Ciaudo group contributes a review to this issue summarizing recent advances of RNAi in stem cell biology focusing on the underlying mechanisms and non-canonical functions of RNAi effector proteins [11].

Last but not least, an original article by the Chambers laboratory provides us with an outstanding example of how stem cells can be used as “model organism” to study the molecular and biochemical functions of proteins [12]. They investigate the function of a key tryptophan repeat within the Nanog pluripotency transcription factor. They show that these residues are essential pluripotency and self-renewal of mESCs, and provide mechanistic insights into how the tryptophan repeat contributes to Nanog homo- (and potentially hetero-) dimerization and thereby to transcriptional activity.

To date, stem cell research centered mainly on developing protocols to produce specific cell types to model diseases and to provide cells for clinical application in tissue regeneration and cell replacement. In this special issue, we provide a new perspective on stem cell biology; that these cells can be used as model system to study the molecular mechanisms of fundamental biology. We envision that extending ESC research to new fields by applying newly developed methodologies (e.g. CRISPR/Cas9 genome editing, proteomics and genomics), then stem cells can become the yeast of the 21st century. In the long term, progress in understanding basic molecular mechanisms will potentially translate into medical applications.

We would like to take the opportunity to thank all the authors and reviewers for their efforts and hope that you will enjoy reading the articles in this special issue as much as we enjoyed editing them!

References

[1] Smith A. Formative pluripotency: the executive phase in a developmental continuum. Development. 2017;144:365-73.
[2] Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature. 1981;292:154-6.
[3] Martin GR. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. Proceedings of the National Academy of Sciences of the United States of America. 1981;78:7634-8.
[4] Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, et al. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145-7.
[5] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663-76.
[6] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861-72.
[7] Fox IJ, Daley GQ, Goldman SA, Huard J, Kamp TJ, Trucco M. Stem cell therapy. Use of differentiated pluripotent stem cells as replacement therapy for treating disease. Science. 2014;345:1247391.
[8] Betschinger J. Charting Developmental Dissolution of Pluripotency. J Mol Biol. 2016.
[9] Ambrosi C, Manzo M, Baubec T. Dynamics and context-dependent roles of DNA methylation. J Mol Biol. 2017.
[10] Festuccia N, Gonzalez I, Navarro P. The Epigenetic Paradox of Pluripotent ES Cells. J Mol Biol. 2016.
[11] Bodak M, Cirera-Salinas D, Luitz J, Ciaudo C. The Role of RNA Interference in Stem Cell Biology: Beyond the Mutant Phenotypes. J Mol Biol. 2017.
[12] Mullin NP, Gagliardi A, Khoa LT, Colby D, Hall-Ponsele E, Rowe AJ, et al. Distinct Contributions of Tryptophan Residues within the Dimerization Domain to Nanog Function. J Mol Biol. 2016.